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SOME RECENT ADVANCES IN OUR KNOWLEDGE OF LEISHMANIASIS.

BY C. M. WENYON.

THE most important recent advances in our knowledge of the diseases due to leishmania have been, firstly, the discovery that a form of Kala Azar, which chiefly attacks young children, occurs along the northern and southern shores of the Mediterranean, and that a form of canine leishmaniasis has an almost identical distribution; and secondly, that the disease long known as "Oriental Sore" occurs in South and Central America. That Infantile Kala Azar occurred in Europe was first demonstrated by Pianese in 1905, who found leishmania in children who had died of the diseases long recognised by Cardarelli, Somma, and Fede as the febrile form of infantile splenic anæmia. In the year before (1904) Laveran found leishmania in films made by Cathoire from the spleen of a nine-month old infant which had died of some ill-defined malady in Goulette (Tunis). In 1908, Nicolle and Cassuto described the first case of Infantile Kala Azar in Tunis, and since that time Nicolle and his collaborators have reported in all twenty-five instances of this disease, which has been recorded also from Algeria by Lemaire and from Tripoli by Tahsim Ibrahim. In Europe, following the discovery of Pianese, Gabbi reported, in 1908, the first case in a child from Messina. In the following years other cases were described by Gabbi from Messina, Feletti and his pupils from Catania, and Jemma from Palermo. Cretien found the disease in Malta, Alvarez in Lisbon, and Gabbi showed that the disease known as Ponos, and occurring in the islands of the Greek Archipelago, was none other than the same Infantile Kala Azar. Owing to the work of Christomanos and others, Infantile Kala Azar is known to be widely spread in Greece and its islands. So that this disease, unsuspected a few years ago, is now known to have a wide distribution along the northern coast of Africa, throughout Greece, Italy as far north as Rome and Sicily, Portugal (Lisbon), Malta, Crete, and many of the small islands around Sicily and Greece, and Marzinowsky has reported the disease from Russia.

This disease, though it specially attacks children of two to three years of age, is not limited to them, as cases in adults have been described by Gabbi (ages 18 and 38), by Fulci and Basile in a youth of nineteen in Rome, by Tahsim Ibrahim in a youth in Tripoli, and in several adults by Christomanos in Greece. However, the number of young children from one to four years of age is well over 90 per cent. of the total number of cases so far recorded, and this is one of the chief points in which there is a difference from the Indian Kala Azar, where the proportion of adults attacked is greater.

The symptoms of Infantile Kala Azar are similar to those of the Indian form of the disease. Usually, the first symptom noted is some gastro-intestinal disturbance accompanied, or not, by slight fever. The child recovers from this first attack, but soon shows signs of failing nutrition. It becomes anæmic, loses flesh, suffers from irregular attacks of fever, while the spleen gradually increases in size and may eventually attain enormous proportions. The liver is enlarged, but to a less extent. When the disease is

well established there is developed a peculiar pallor of the skin, which Nicolle describes as being so characteristic that one may suspect the disease from this sign alone. The child, if old enough to run about, ceases to do so, and no longer joins in the games of its comrades ; it becomes more and more emaciated, while the abdomen becomes increasingly prominent; the attacks of fever, which conform to no known type and are unaffected by administration of quinine, are more numerous, while the onset of an enterocollitis may threaten the life of the patient. Transitory œdemas about the limbs and face are frequently noted, and punctiform hæmorrhages in the skin are often seen. A condition of hæmophilia with bleeding from the bowel, gums, or nose may develop, and this may be so severe as to cause the death of the child. Ulceration of the intestine as shown by dysenteric symptoms, ulceration about the gums and lips sometimes developing into noma, may contribute to bring about a fatal issue. Death results, as a rule, from the onset of broncho-pneumonia or severe diarrhœa or dysentery. Nicolle has reported several cases where death was due apparently to the sudden onset of a dyspnœa, possibly due to an œdema of the glottis. In other cases it results from severe hæmorrhage from the nose or bowel or the toxic effects of noma. The symptom of fever is apparently never wanting, and its great feature is its irregularity. There occurs febrile periods alternating with periods of apyrexia. During the febrile periods the fever may be intermittent or remittent, and it may suddenly change from one of these types to the other. There may be two or three elevations of temperature in the twenty-four hours. Occasionally the onset of fever is accompanied by rigor and followed by sweating. During one febrile period the type of fever may be quite different from the type it will follow in the next period.

A blood examination shows a reduction in the number of red blood corpuscles, which may fall as low as 1,250,000, while the hæmoglobin reduction is usually in the same proportion. The number of white corpuscles varies very much, for though it is often normal, or above normal, most usually there is slight leucopœnia in which the proportion of mononuclears is increased.

The duration of the disease varies considerably. Sometimes the course is exceedingly rapid, and death may result within forty days of the first noticeable sign. Usually the disease develops more slowly and may last two, three, or four years. The disease is not invariably fatal, as several cases of spontaneous recovery have been reported.

As regards the diagnosis, most observers are agreed that the discovery of the parasite is the only sure means of attaining this end. Nicolle has found the parasites in the blood of the peripheral circulation by a method of centrifugation, but, as a rule, this method gives a positive result in only a small percentage of cases. Spleen puncture is the method most usually employed, though Pianese has removed marrow from the head of the tibia. Nicolle, who has had a great experience in this disease in Tunis, remarks that spleen puncture may be performed with ordinary precautions without danger, and he has repeated the puncture several times in some of his cases.

Within the body the parasites are to be found in greatest number in the spleen, bone-marrow, and liver. They may also be found in the kidneys, lungs, lymphatic glands, intestines, and exceptionally in the muscles. They occur in large mononuclear cells or macrophages, which are possibly derived from the endothelium of the blood capillaries.

As regards its structure, the leishmania of Infantile Kala Azar does not

differ in any way from that of the Indian form of the disease. It is culturable in citrated blood, the medium of Novy and MacNeal, the modified blood agar of Nicolle, or the sterilised blood agar of Mathis. In these cultures the parasite is found to develop into a flagellated organism of the Herpetomonas type.

A point of great interest in connection with the Infantile Kala Azar is its almost constant association with a form of leishmaniasis in dogs. In practically all the great centres of Infantile Kala Azar—viz., Tunis, Algeria, Lisbon, Malta, Sicily, Rome, Greece—the ordinary domestic dog has been found to be liable to this disease. This fact was first demonstrated by Nicolle in Tunis, and he propounded the theory of the canine origin of human Kala Azar and suggested that the dog, in which the disease may be exceedingly mild or latent, acts as a reservoir for the virus, which is transmitted to man by some biting arthropod. Basile, working in Sicily and Italy, claims to have proved that it is by means of the dog flea (*Ctenocephalus canis*) and the domestic flea (*Pulex irritans*) that the disease is transmitted amongst dogs and from them to man. Basile's experiments are of four kinds. First, he introduced uninfected dogs into houses in which Kala Azar cases occurred, and states that the dogs contracted the disease: secondly, healthy dogs were made to live in close association with an infected dog on which were many fleas; these dogs also became infected: thirdly, fleas taken from infected houses in Bordonaro, in Sicily, were transported to Rome and there placed upon uninfected and isolated dogs, which very soon became infected: and fourthly, the dog flea (*Ctenocephalus canis*) fed upon spleen-juice from an infected dog is found to become infected with cultural forms of leishmania. The gut-contents of the fleas are infective to healthy dogs. Basile claims to have taken every precaution to exclude errors from his experiments and to have thus established that the flea is the transmitting agent of human and canine Kala Azar. The experiments of Basile have, however, been severely criticised by Gabbi, who has failed to confirm these results. On the other hand, owing to the results of Franchini, who has infected Anophelines by feeding them on cultures of leishmania, Gabbi is inclined to incriminate the mosquito as being the bearer of this disease. Basile in Sicily, Sangiorgi in Turin, where canine leishmaniasis has recently been discovered, and Alvarez in Lisbon, have found in fleas taken from infected dogs flagellates which they claim to be developmental forms of leishmania. These observers declare that fleas which have not had an opportunity of sucking infected blood are found to be free from these flagellates. Though in experiments of this nature one has to be exceedingly cautious in judging of the significance of intestinal flagellates of insects, which, as every one knows, may be simply harmless parasites peculiar to the insect in question, still there is no *à priori* reason why leishmania should not develop in the intestine of the flea or that the flea should not be able to transmit the disease. However, these interesting experiments need further confirmation. It may be mentioned that Sangiorgi, in Turin, noted that a dog which had been living in close contact with an infected dog contracted the disease, and that Marshall, in the Sudan, has had a similar experience, though in this case with an uninfected monkey which was caged with others suffering from the disease.

Experimental inoculation of Infantile Kala Azar was first accomplished by Nicolle in Tunis, who found that both dogs and monkeys could be infected by intraperitoneal or intrahepatic injection of material obtained from cases of the disease. The disease in monkeys resembles that in children more

closely than does the disease in dogs, in which it may be exceedingly mild. As a rule, other animals are not infected, though a slight and transitory infection may take place in guinea-pigs and rats. The Infantile Kala Azar of Sicily and Italy is equally inoculable into dogs and monkeys, and in one case Franchini produced a fatal infection in a guinea-pig ; and Volpino inoculated a rabbit in the cornea with the result that there was produced a local infection resembling the lesion of Oriental Sore. In Lisbon, Alvarez has also infected dogs. The ease with which the Mediterranean disease is inoculable into dogs has been raised as an argument against the identity of this disease and that of India. Though inoculation of dogs in India has been attempted, the number of experiments is limited and they were not exhaustive. In this connection Nicolle remarks that when two such dissimilar diseases as Infantile Kala Azar and Oriental Sore are inoculable to dogs one would be very much surprised to find that Indian Kala Azar, so similar to the Infantile disease, could not thus be reproduced.

Kala Azar, first shown to occur in the Sudan by Neave, has been found, through the investigations of Bousfield, Marshall, and Thomson, to be widely distributed along the Blue Nile and occurring in the Sennar and Kassala Provinces. In Sennar the disease attacks children with an average age of twelve years, while in Kassala adults are more often affected. A feature of the investigations of the disease in Sennar is the discovery of leishmania in the peripheral blood of 86·6 per cent. of the cases. Marshall has been able to reproduce the disease in monkeys, but so far has not found spontaneous infection of dogs nor has he infected dogs by inoculation.

Though of recent years there has been much advance in our knowledge of the distribution of Kala Azar and the discovery of the disease in dogs which opens up the possibility of their acting as reservoir hosts, little progress has been made in the way of treatment, though most of the important remedies which have been tried for sleeping sickness have here been employed. It is true, however, that certain cases may recover spontaneously; and in this fact Nicolle finds encouragement, since, in his opinion, it shows that the human organism is naturally resistant to a certain extent, and that it needs only the assistance of some therapeutic agent to overcome the parasite. What this agent is still remains to be discovered.

Oriental Sore, up till a few years ago, was thought to be limited to the East, as its name implies. It had been known for years in India, Persia, Asiatic Turkey, Russia, and Northern Africa. It has recently been described from Italy, Sicily, and Greece, and several cases have been recorded from New Caledonia. In 1909 Lindenberg and Carini and Paranhos demonstrated leishmania in an ulcer in Brazil. In the same year Tonin, Heckenroth, and Natan-Larrier established the fact that the disease known as Pian-Bois in French Guiana was a form of dermal leishmaniasis. The disease was then described from Manaos on the Amazon and by Darling in Panama.

Carini and Splendore have lately called attention to the fact that the leishmania may not only infect the skin but that the disease may occur in the mouth and nose, producing therein extensive ulceration and tissue destruction. In most of these cases there is some primary skin-infection, the disease spreading thence to the buccal and nasal cavities. In some cases, however, it is stated that the primary lesion may be in the mouth. This form of leishmaniasis occurs side by side with a form of mycotic infection of the mouth and nose, and the two diseases are readily confused. Diagnosis is made by

the discovery of leishmania in the exudation from the ulcers or vegetations in the mouth.

Flu has recently described the disease which occurs in the three Guianas under the names of Forest-Yaws, Boch-Yaws, or Pian-Bois. This is a leishmaniasis, and effects chiefly the skin on exposed parts of the body. It corresponds in many ways with the Oriental Sore of the East, and the author is convinced that the disease is the result of the bite of a tick, as only those who have been working in the bush where ticks abound become infected. The author, however, brings forward no experimental proof of his contention, though the earliest lesion of the disease resembles very closely the wound inflicted by the tick.

Experimental work on Oriental Sore has been undertaken by Nicolle and Manceaux. These authorities have discovered that Oriental Sore may be reproduced in dogs and monkeys by inoculating the skin about the ears, eyes, and nose. The resulting lesion resembles the typical sore in man, but endures a shorter time. They bring forward a certain amount of evidence to show that animals which have recovered from an infection of Kala Azar are immune against the organism of Oriental Sore.

Culture of the parasite of Oriental Sore (*Leishmania tropica*) was first obtained by Nicolle on blood agar. These cultures remain infective and give rise to sores when inoculated into skin of man, monkeys, and dogs. Intrahepatic and intraperitoneal injection of large quantities of culture of *Leishmania tropica* into dogs does not bring about any general infection, though Novy has shown that similar inoculation of dogs with cultures of the leishmania of Infantile Kala Azar gives rise to the disease.

As regards the transmission of Oriental Sore no conclusive results have been obtained. Most observers agree that the house-fly must play some part in this transmission ; and Row has found that the parasite may remain infective for monkeys for three hours after they have been taken up by the fly, and suggests that the parasites may in this way be passed in the fæces on to some abrasion of the skin and give rise to the disease. Working on the Bagdad Sore the present writer found that bed-bugs and *Stegomyia fasciata* would feed from the sore and that in so doing parasites were taken up. In the guts of these arthropods the parasites underwent a development into flagellate forms as they do in cultures. Attempts at transmitting the disease to himself by the bites of *Stegomyia fasciata* previously fed upon the sore were unsuccessful, as were also a limited number of similar experiments conducted later in Aleppo with *Phlebotomus*.

The exact relation of Oriental Sore to Kala Azar is still doubtful. Some authorities maintain that the one disease is in reality a mild form of the other produced by an altered or attenuated virus, while others claim that the organisms are quite distinct though resembling one another morphologically. Still more difficult is the question of the relation of the Indian to the Mediterranean Kala Azar. In symptomatology there is a great similarity in the two diseases. The Indian disease is generally more rapidly fatal than the Mediterranean form, though, as already mentioned, this may be fatal in forty days from the onset of the disease. A further difference is the fact that in the West young children of from one to four years of age are most usually attacked, while in India adults are most commonly affected. This discrepancy may be due to the difference in the conditions of life in the two parts of the world and the possible difficulty of obtaining information as regards young children in India. The fact that dogs are so readily infected with the

Infantile Kala Azar while they are apparently refractory to the Indian disease has been frequently raised as an argument against the identity of the two diseases. The Indian experiments, however, need repeating and extending, for it may be that the pariah dog of India is immune, as is suggested by the failure to find any case of spontaneous leishmaniasis in Indian dogs, though over one thousand were examined by Donovan. It will be necessary to inoculate dogs with the Indian parasite under the same conditions as those which are successful in the Mediterranean disease. Till this work is done it is impossible to decide finally whether the two diseases are identical or not. Cases of Kala Azar have been reported from Russia, and Sluka has described a case from Tashkent in Turkestan. It is probable that with further observation the disease will be found to have a wider and extending distribution, so that the idea that any extensive barriers separate the endemic centres of Europe, India, China, and the Sudan will have to be given up.